What Type of Drug Could be Antiarrhythmic in Acute Myocardial Ischemia? Insights from Simulations

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Acute myocardial ischemia (AMI) may lead to potentially lethal arrhythmias. Hyperkalemia constitutes a major contributing factor, increasing the likelihood of unidirectional block and subsequent reentry. Along with acidosis and anoxia, it also produces dynamic changes in action potential morphology. This heterogeneity during the AMI process creates a vulnerable window (VW) where re-entry due to an ectopic stimulus can be generated. However, there is no drug specifically designed to effectively address the electrophysiological and arrhythmogenic consequences of ischemic pathology. According to our previous work at the cellular level, such ideal drug should have calcium channel blocker characteristics. Therefore, this work aims to study the effect of calcium channel blockade on the efficacy of drugs to reduce the VW and prevent arrhythmias during AMI using 3D computational simulations. A modified version of the O'Hara et al. computational model was used, which includes the effects of AMI and drugs. Simulations were carried out on a biventricular 3D anatomical model including a realistic geometry of the ischemic region and borderzone. It also includes transmural heterogeneity and anisotropy (Fig 1A). The results suggest a biphasic behavior in the effect of calcium blockade on VWs: a small or large blockade promotes anti-arrhythmic tendencies, while an intermediate blockade is highly pro-arrhythmic compared to control (Fig 1B). The results show that the control has a peak VW of 55 ms with a width of 12 minutes, while the blocking percentages of 20, 40 and 60% have a peak of 90, 160 and 35 ms and a width of 8, 10 and 6 minutes, respectively. In conclusion, the work demonstrates the feasibility of in-silico experiments to perform classification and test the efficacy of drugs to minimize vulnerability to arrhythmias in AMI.

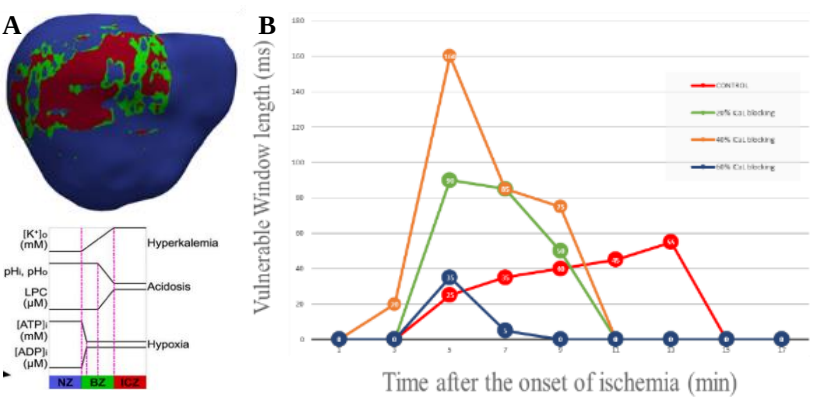

Figure 1. (A) Ischemic regions (B) Vulnerable window calculated for different minutes after the onset of ischemia. The control is marked in red. Blockade of 20%, 40% and 60% of calcium channels are marked in green, orange, and blue respectively.